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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C07H 21/00, 21/02, 21/04, A61K 31/175, 31/335, 31/47, 31/70		A1	(11) International Publication Number: WO 98/18810 (43) International Publication Date: 7 May 1998 (07.05.98)
(21) International Application Number: PCT/US97/19791 (22) International Filing Date: 30 October 1997 (30.10.97) (30) Priority Data: 08/738,652 30 October 1996 (30.10.96) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 08/738,652 (CIP) Filed on 30 October 1996 (30.10.96) (71) Applicant (for all designated States except US): THE UNIVERSITY OF IOWA RESEARCH FOUNDATION [US/US]; 214 Technology Innovation Center, Oakdale Research Campus, Iowa City, IA 52242 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): KRIEG, Arthur, M. [US/US]; 890 Park Place, Iowa City, IA 52246 (US). KLINE, Joel, N. [US/US]; 552 Linder Road, N.E., Iowa City, IA 52242 (US). (74) Agent: HAILE, Lisa, A.; Fish & Richardson P.C., Suite 1400, 4225 Executive Square, La Jolla, CA 92037 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: IMMUNOSTIMULATORY NUCLEIC ACID MOLECULES			
(57) Abstract Nucleic acid sequences containing unmethylated CpG dinucleotides that modulate an immune response including stimulating a Th1 pattern of immune activation, cytokine production, NK lytic activity, and B cell proliferation are disclosed. The sequences are also useful as synthetic adjuvant.			

*(Referred to in PCT Gazette No. 38/1998, Section II)

BNSOOCID: <WO_9818810A1_IA>

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FIGURE 2

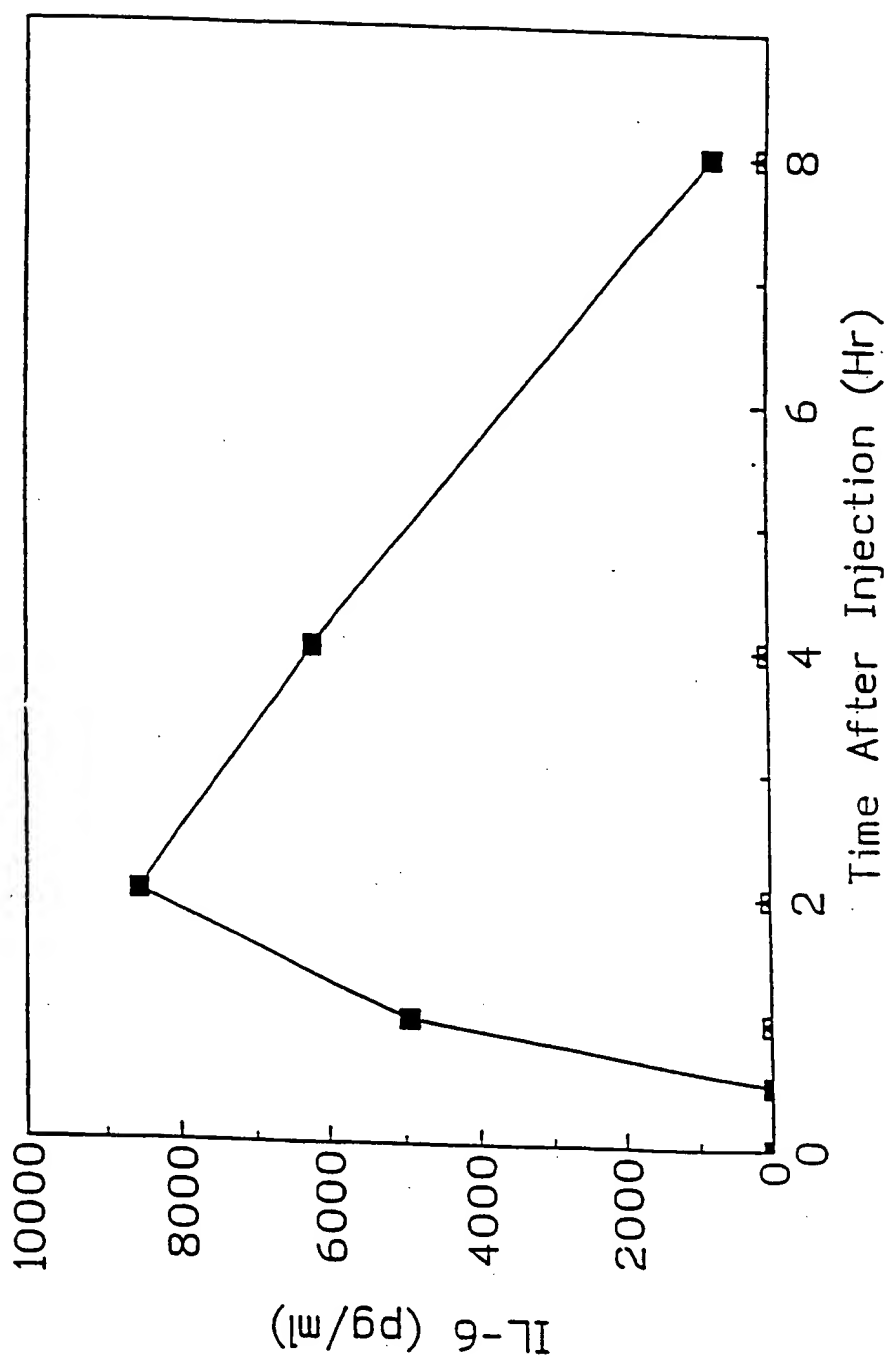


FIGURE 3

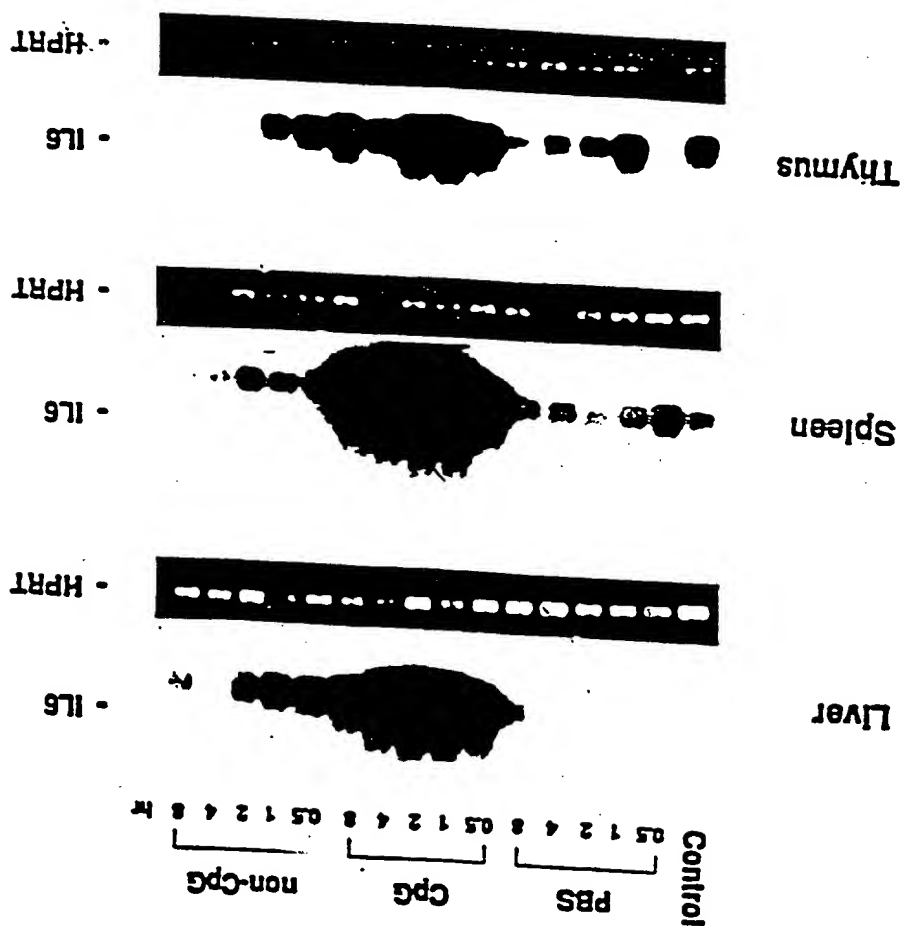


FIGURE 4A

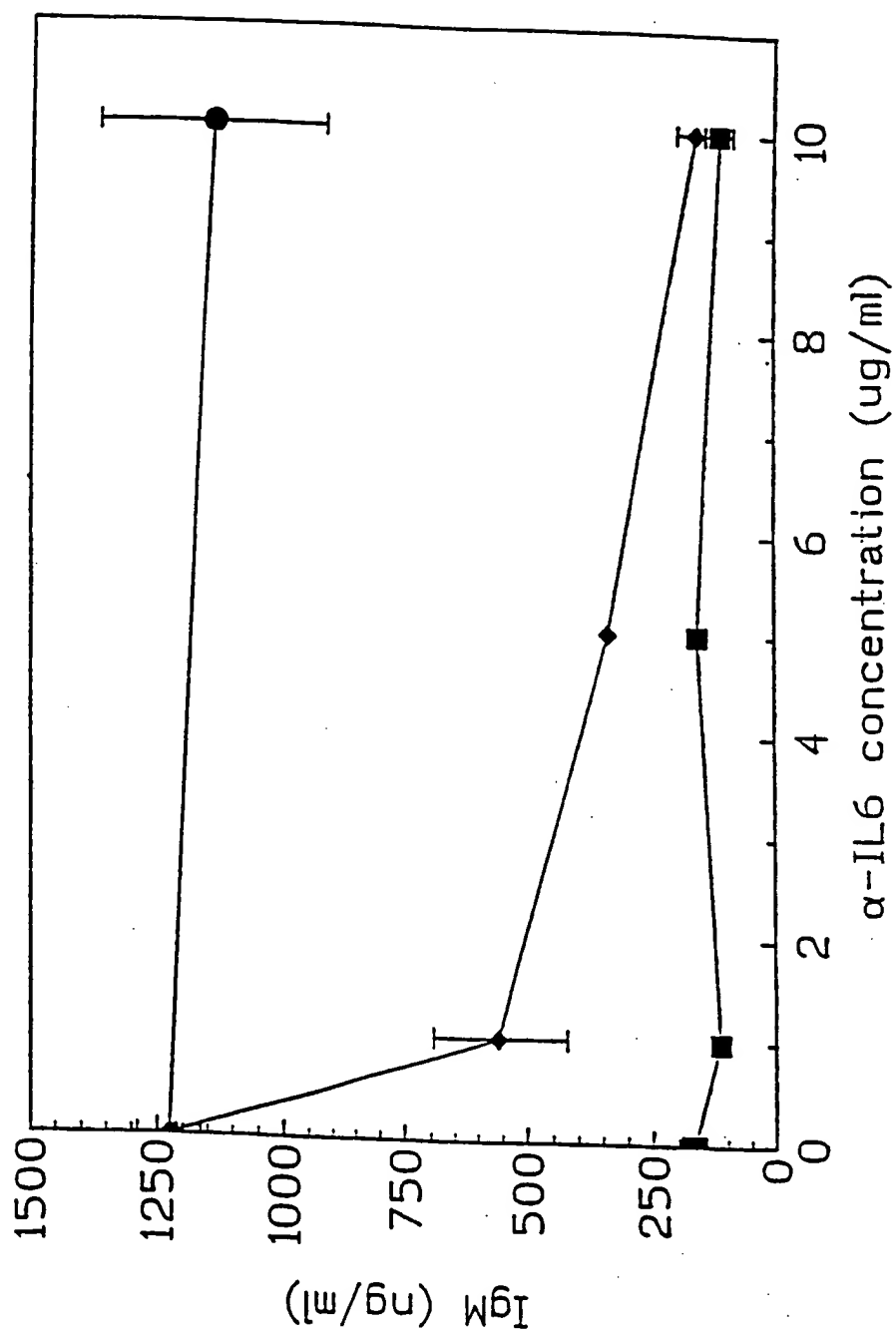
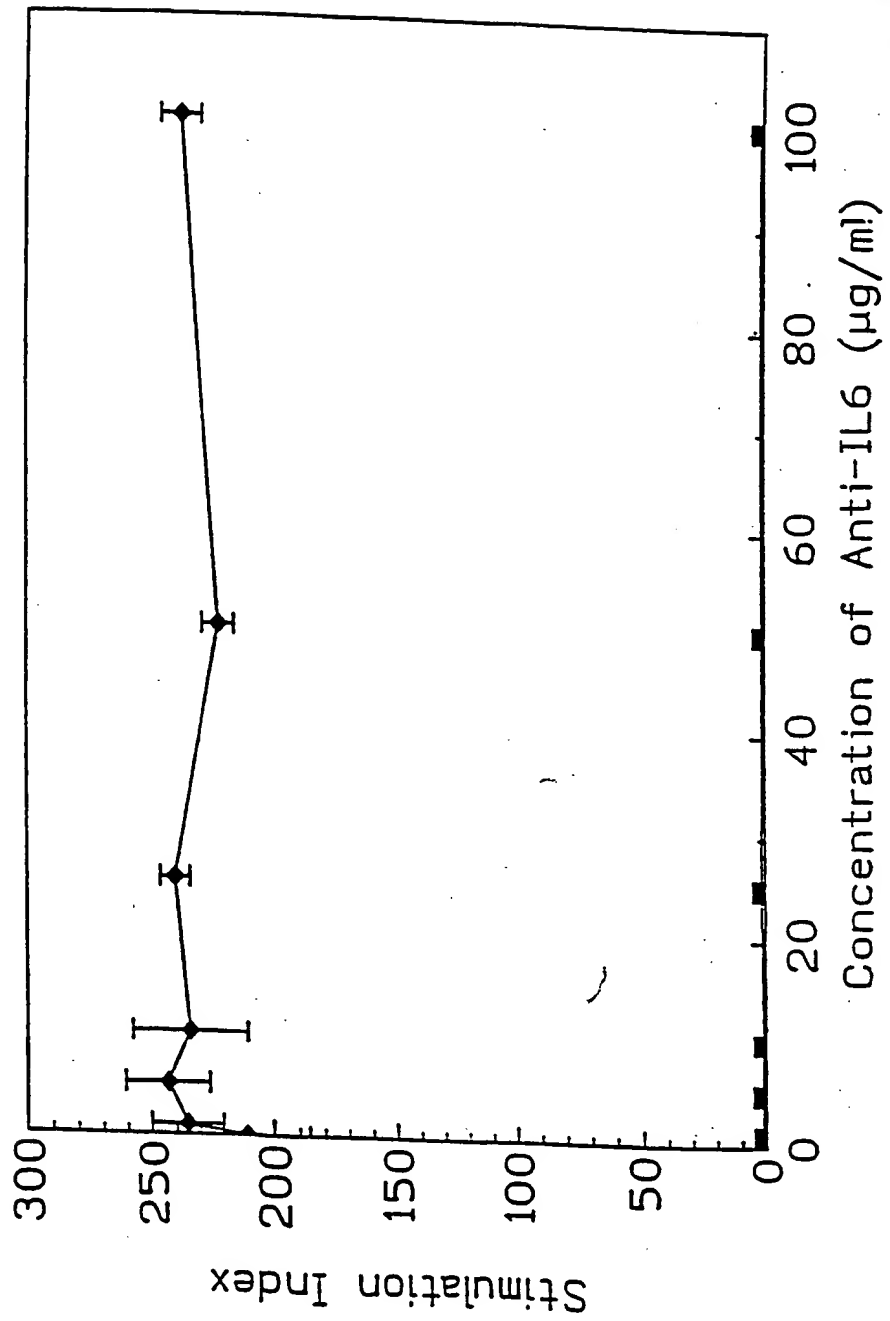


FIGURE 4B



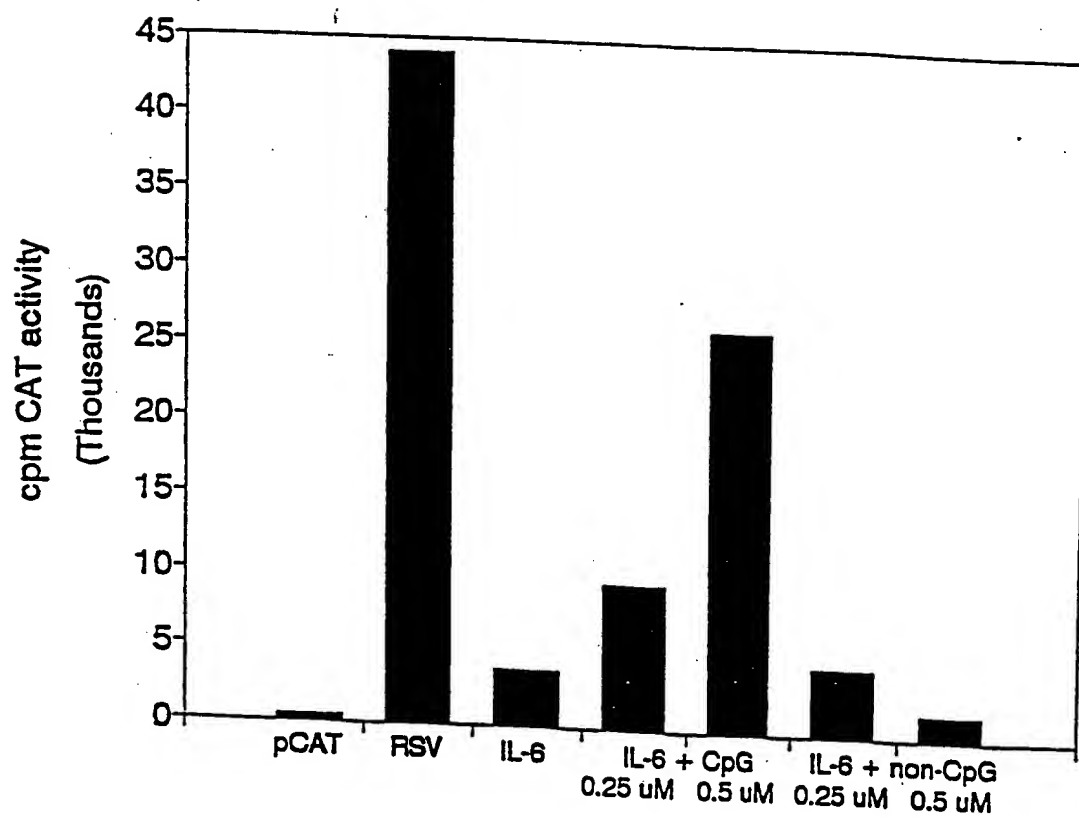


FIGURE 5

FIGURE 6

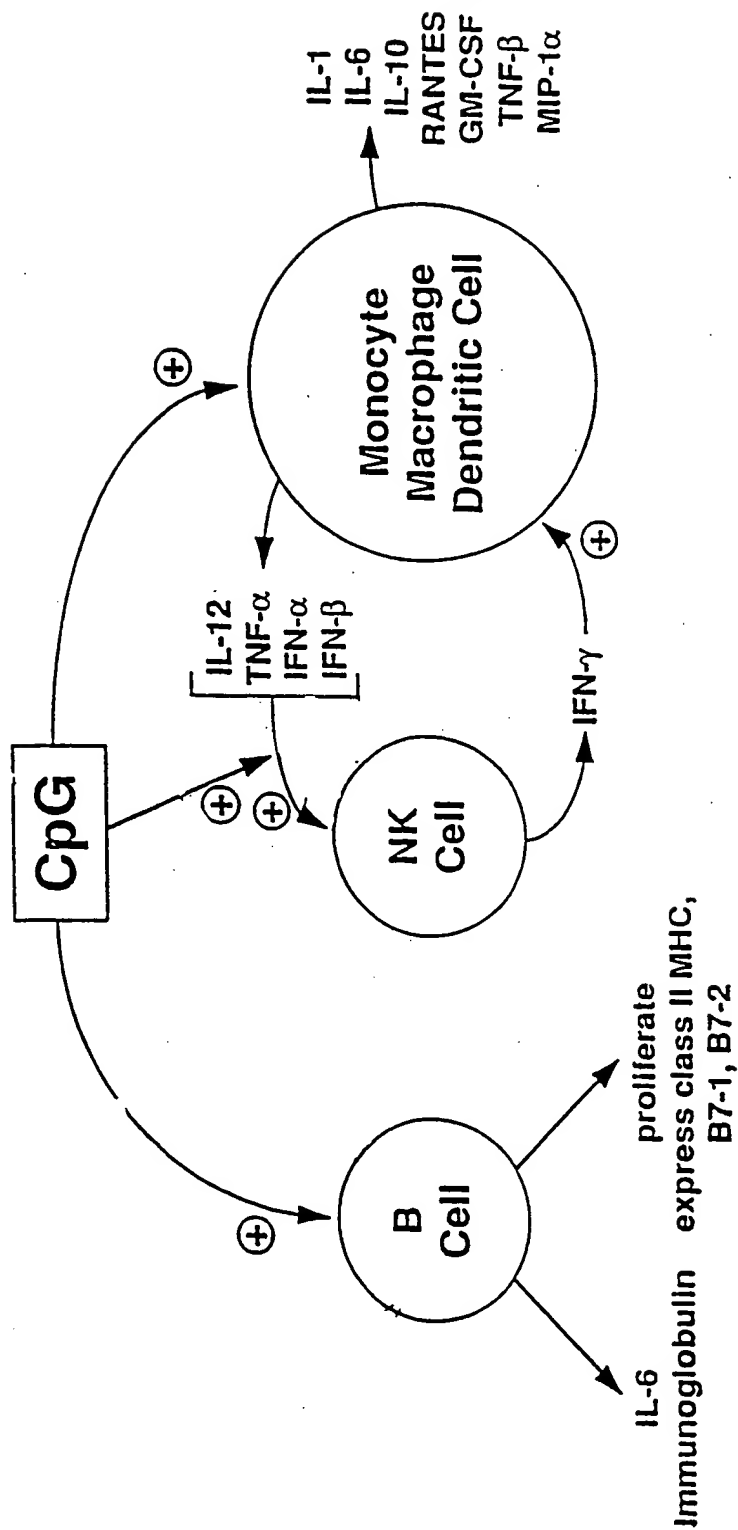


FIGURE 7

Timing of NF κ B Activation in Monocytes treated with E. coli DNA

Treatment:	0	EC DNA	CT DNA	LPS
min:	0	15 30 15 30	15 30	15 30

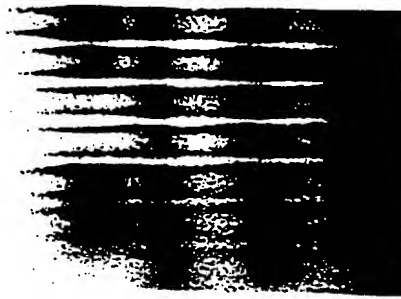
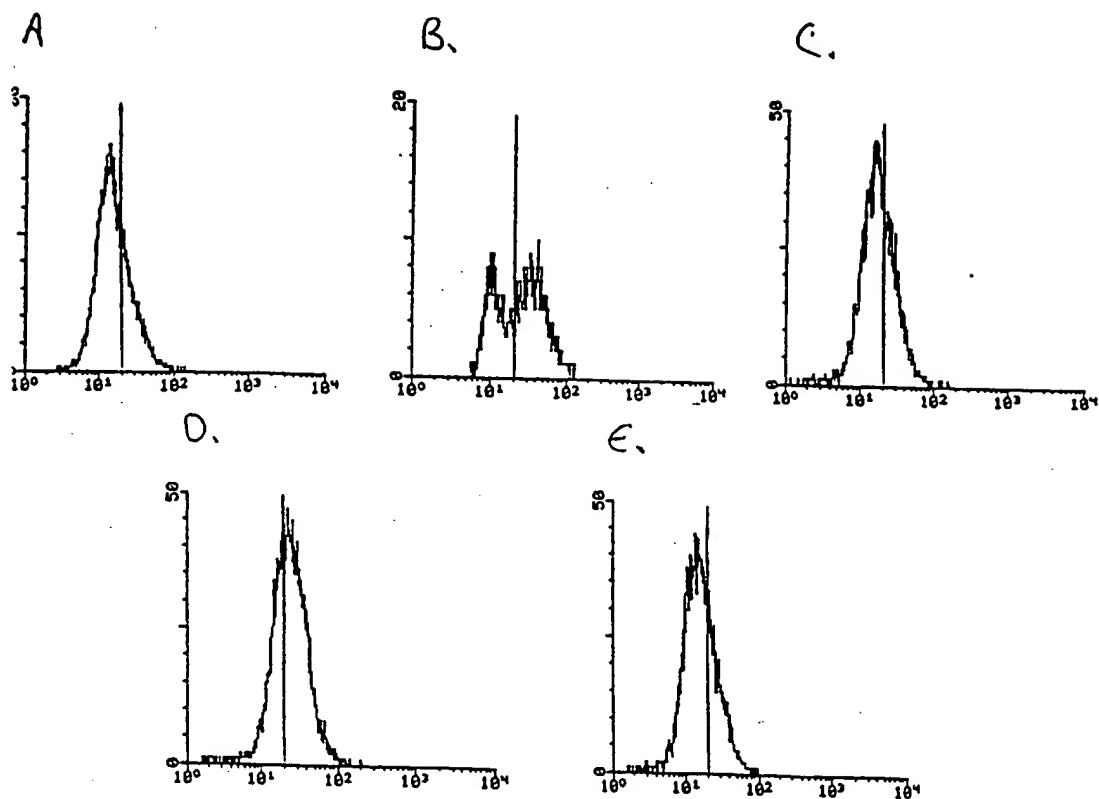


FIGURE 8 A



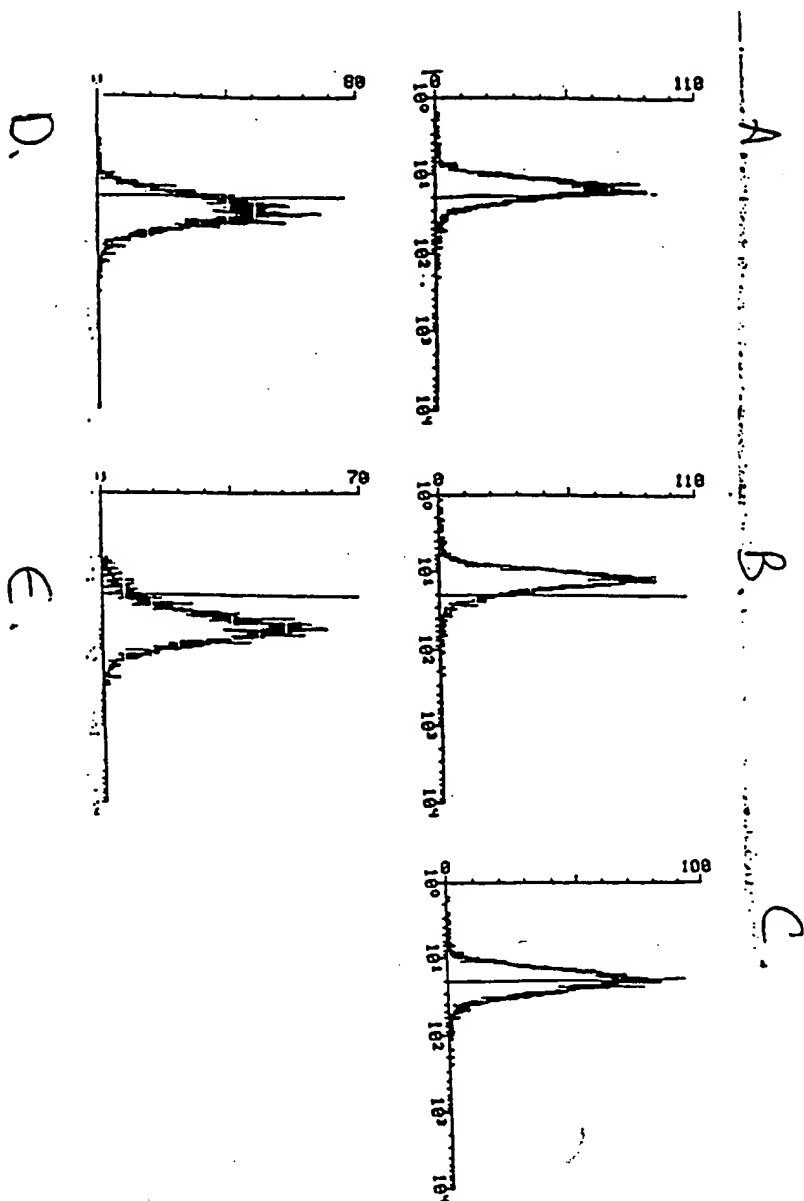


FIGURE 8B

FIGURE 9

Effect of CpG and Airway Exposure on Lung Lavage Cell Count

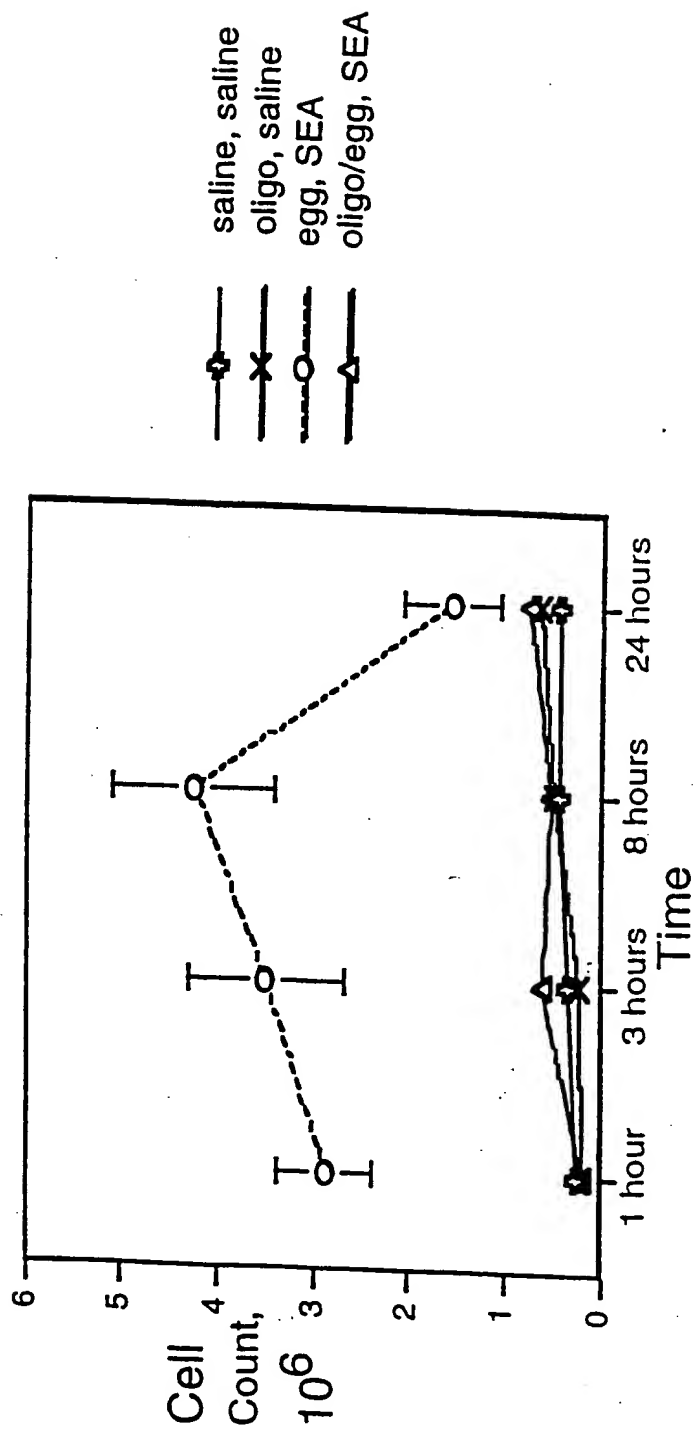


FIGURE 10

Effect of CpG and Airway Exposure on Lung Lavage Eosinophil Count

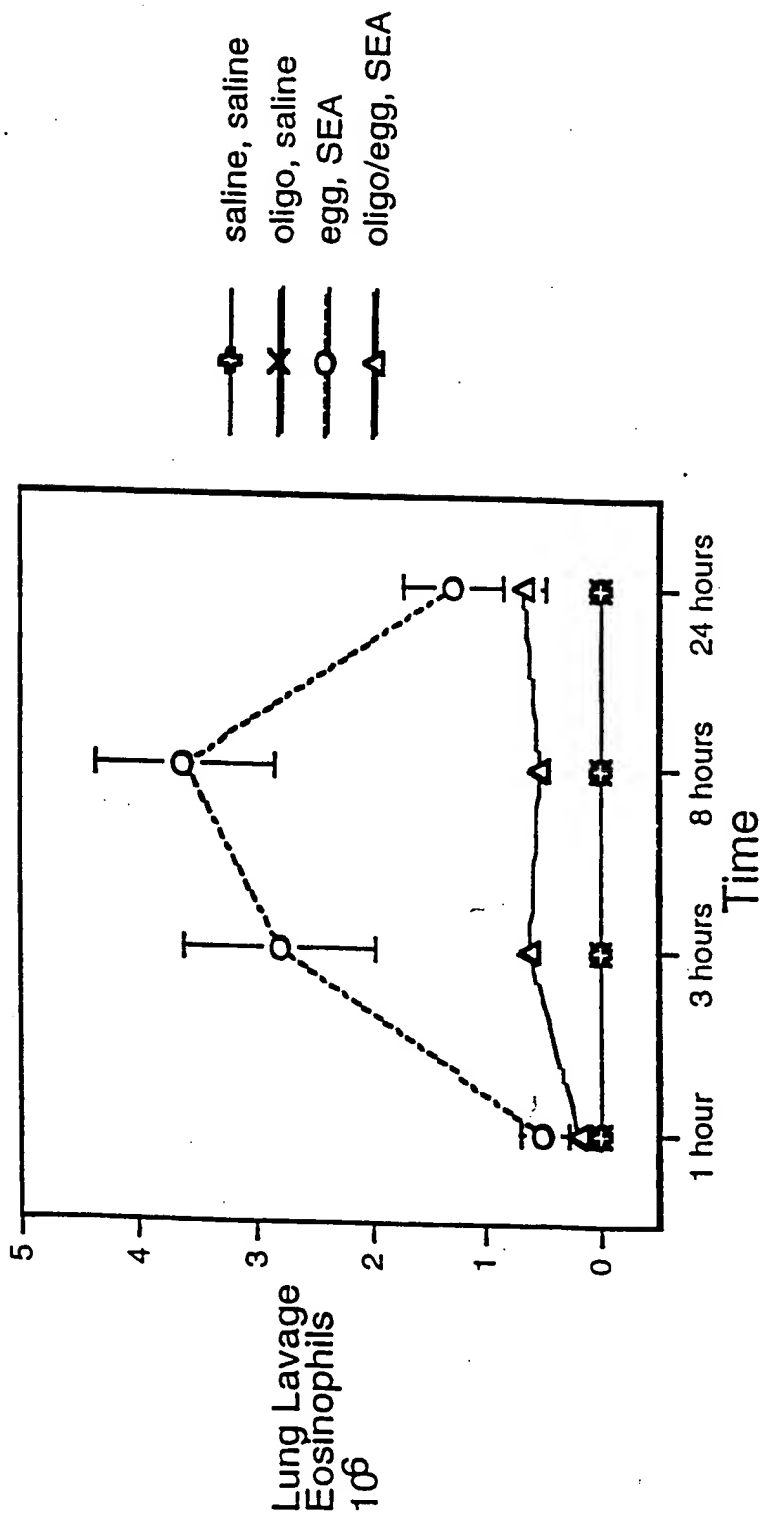


FIGURE 11

Effect of CpG and Airway Exposure on Lung Lavage Differential

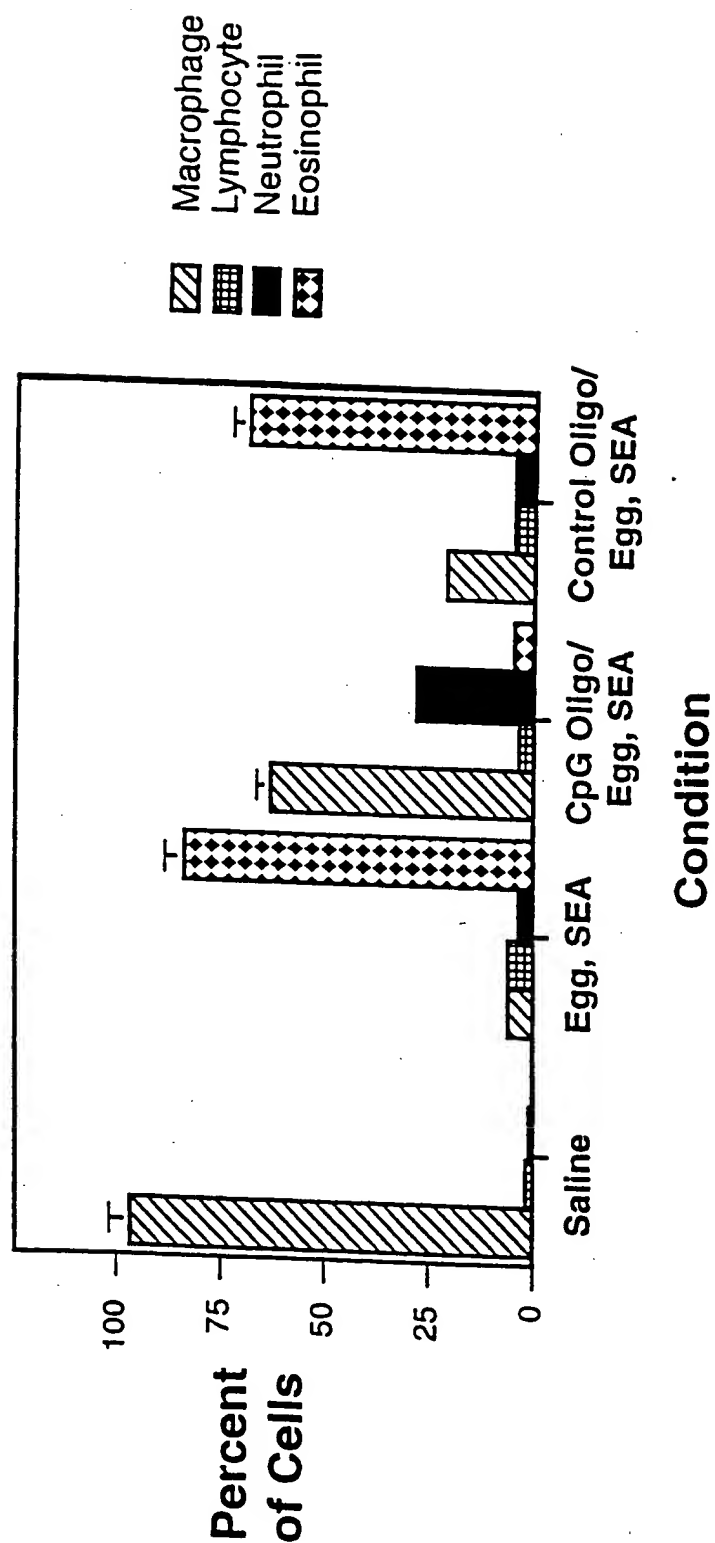


FIGURE 12

Effect of Oligonucleotide Dose on Total and Eosinophil Cell Counts

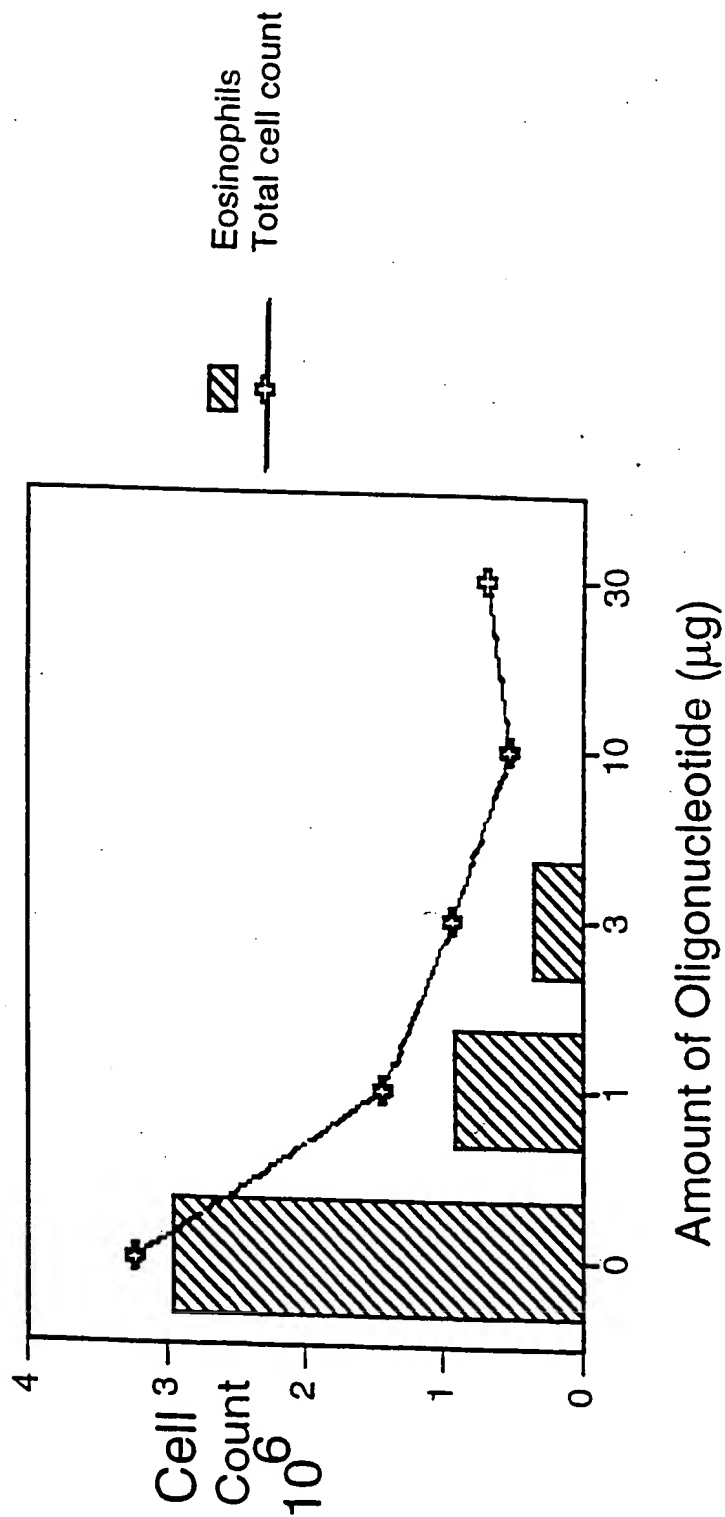


FIGURE 13

Effect of CpG and Airway Exposure on Lung Lavage IL-4

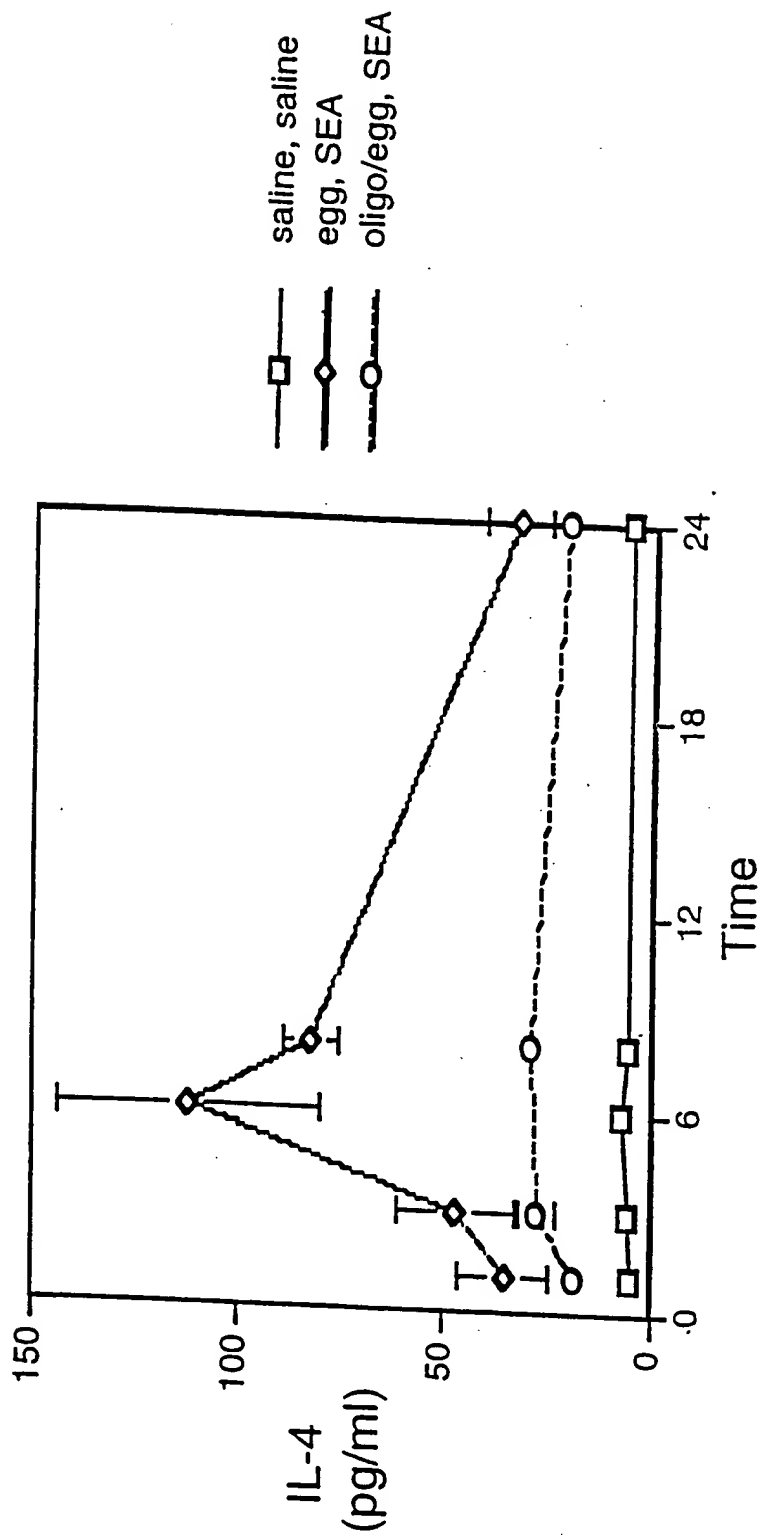
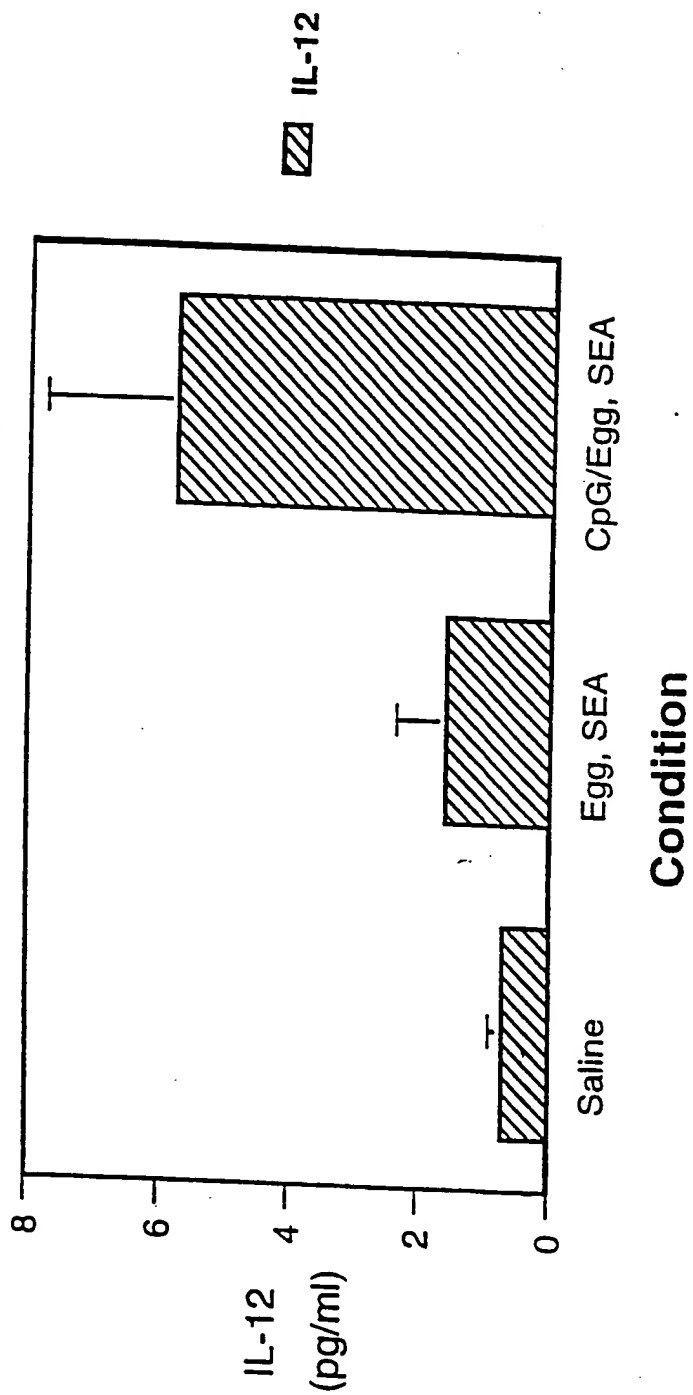


FIGURE 14

Effect of CpG and Airway Exposure on Lung Lavage IL-12

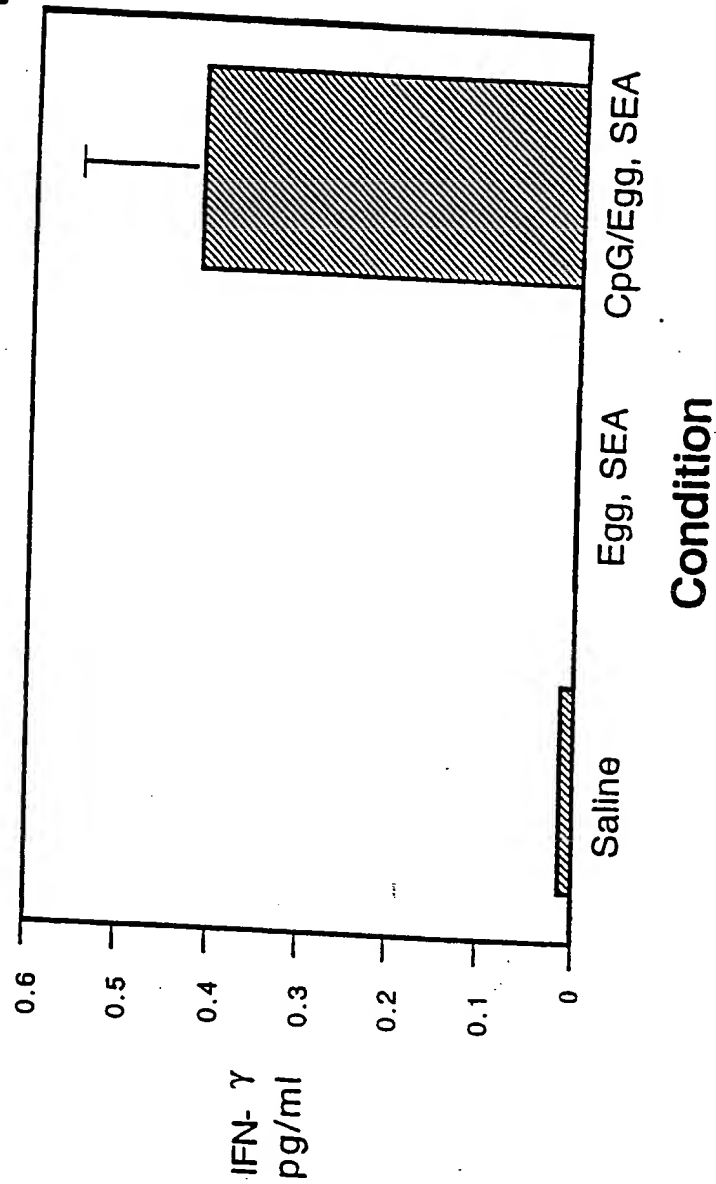


19/19

IFN- γ

FIGURE 15

Effect of CpG and Airway Exposure on Lung Lavage IFN- γ



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19791

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C07H 21/00, 21/02, 21/04; A61K 31/175, 31/335, 31/47, 31/70

US CL : 536/23.1; 514/44, 450, 313, 23

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1; 514/44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FOX, R.I., Mechanism of action of hydroxychloroquine as an antirheumatic drug, Chemical Abstracts, 29 April 1994, Vol. 120, No. 15, Abstract No. 182630, see entire document.	36-41
Y	WO 9602555 A1 (THE UNIVERSITY OF IOWA RESEARCH FOUNDATION) 01 February 1996, see entire document.	23 and 26
Y	BLAXTER, M.L., et al, Genes expressed in Brugia malayi infective third stage larvae, Molecular and Biochemical Parasitology, April 1996, Vol. 77, pages 77-93, see entire document.	26

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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14 JANUARY 1998

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INTERNATIONAL SEARCH REPORT

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MOTTRAM, J.C., et al, A novel CDC2-related protien kinase from <i>Leishmania mexicana</i> , LmmCRK1, is post-translationally regulated during the life cycle, <i>J. Biol. Chem.</i> October 1993, Vol. 268, No. 28, pagess 21044-21052, see entire document.	26
Y	SCHNELL, N., et al, Identification and characterization of a <i>Saccharomyces cerevisiae</i> gene (PAR1) conferring resistance to iron chelators, <i>Eur. J. Biochem.</i> , 1991, Vol. 200, pages 487-493, see entire document.	26 and 29
Y	WALLACE, R.B., et al, Oligonucleotide probes for the screening of recombinant DNA libraries, <i>Methods in Enzymology</i> , 1987, Vol. 152, pages 432-442, see entire document.	23, 26, and 29

Form PCT/ISA/210 (continuation of second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19791

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-3,9-22,24,25,27,28,30,31,33 & 34
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1))(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/19791

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

STN, APS, Nucleic Acid Sequence Databases, bafilomycin#, chloroquine#, monensin#, lupus(w)erythematosus, sepsis, inflammatory(w)bowel(w)disease#, psoriasis, gingivitis, arthritis, crohn(w)disease, grave(w)disease, asthma#

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

The claims embrace an astronomical number of embodiments coupled with negative limitations such that no meaningful search of nucleotide sequence databanks can be made. For example, claim 1 wherein N1 + N2 is 22-26 embraces about 36,000,000,000,000,000 embodiments except for those embodiments wherein N1 and N2 do not contain CCGG or more than one CCG or CGG trimer.